Regulatory Pathways: NDA Process

Kim Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs

What information is required for an NDA?

- Form 356h
  http://www.fda.gov/opacom/morechoices/fdaforms/cder.html

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(if previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*		CODE NAME *(if any)*
DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, DMFs, and DMFs referenced in the current application)

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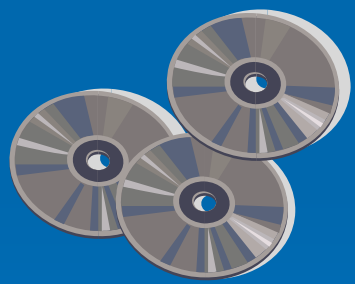
What information is required for an NDA?

- Form 356h
  http://www.fda.gov/opacom/morechoices/fdaforms/cder.html
- Index
- Summary (including labeling, *marketing history*, technical sections)
- Technical sections (chemistry, nonclinical pharm/tox, human pharmacokinetics, statistical)
- Other (pediatrics, patent information, financial disclosure, etc.)

Code of Federal Regulations: 21 CFR 314.50
http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200421

What is an acceptable format for an NDA?

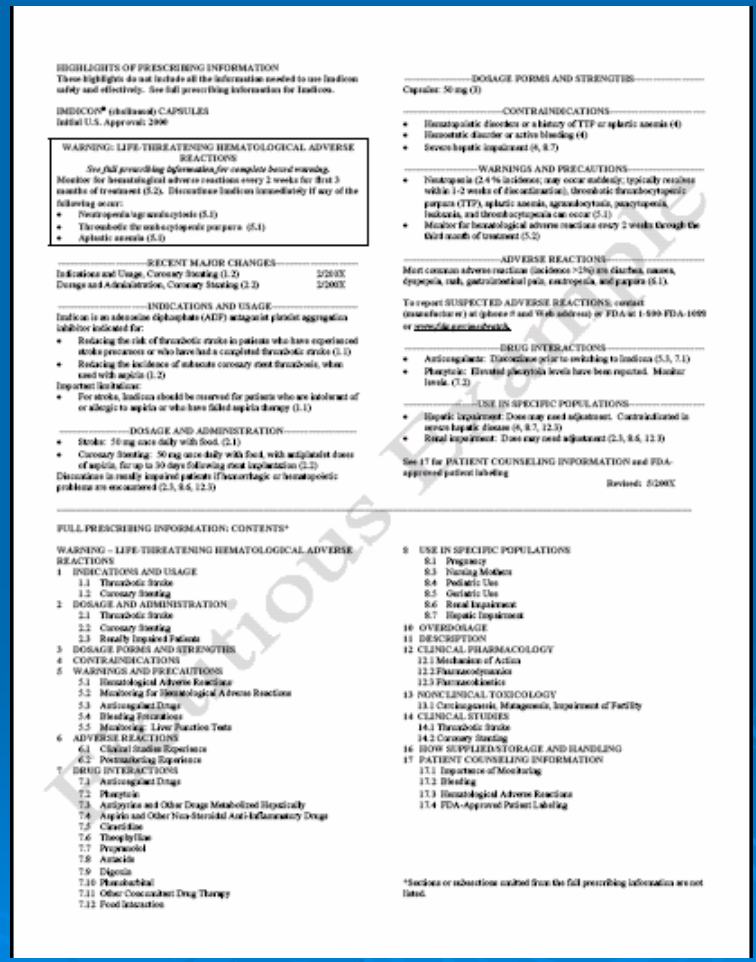
- "Traditional" or "International" (Common Technical Document or CTD)
- Paper or Electronic or Mixed



http://www.fda.gov/cder/about/smallbiz/default.htm

Did you know… Prescription labeling has a whole new look!

- Effective June 30, 2006, all new applications must be in the new format
  - Highlights
  - Table of contents



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON® (ibalmandy) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:

- Neutropenia/agranulocytosis (5.1)
- Thrombotic thrombocytopenic purpura (5.1)
- Aplastic anemia (5.1)

RECENT MAJOR CHANGES

Indications and Usage, Coronary Stenting (1.2) 2/2006
Dosage and Administration, Coronary Stenting (2.2) 2/2006

INDICATIONS AND USAGE

Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:

- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:

- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

DOSAGE AND ADMINISTRATION

- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet dose of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg (3)

CONTRAINDICATIONS

- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (6, 8.7)

WARNINGS AND PRECAUTIONS

- Neutropenia (2.4 % incidence; may occur suddenly, typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

USE IN SPECIFIC POPULATIONS

- Hepatic Impairment: Does may need adjustment. Contraindicated in severe hepatic disease (6, 8.7, 12.3)
- Renal Impairment: Does may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/2005

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

http://www.fda.gov/cder/regulatory/physLabel/default.htm

What is the difference between a 505(b)(1) and 505(b)(2) NDA?

- The standard for approval (substantial evidence of safety and effectiveness) is the same
- The *source* of data is different
  - 505(b)(1) – your data (you did the studies or you own the data) or you have right of reference (permission) to use the data
  - 505(b)(2) – relies upon data you don't own or have right of reference to, including published literature

What are some examples of products submitted as 505(b)(2) NDAs?

- Change from a previously approved drug in:
  - Dosage form
  - Formulation
  - Strength,
  - Route of administration
  - Dosing regimen
  - Indication
  - Active ingredient (e.g., different salt)

What are some examples of products submitted as 505(b)(2) NDAs?

- Substitution of an active ingredient in a combination product
- A combination of two previously approved products
- Monograph deviation

Guidance for Industry, Applications Covered by Section 505(b)(2)

http://www.fda.gov/cder/guidance/2853dft.htm

Response to Citizen Petition:

http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf

What makes a 505(b)(2) NDA “special”?

- It can rely upon “general” information (e.g., non-product specific published literature)
- It can rely upon our previous finding of safety and efficacy (i.e., a previously approved product)
  - Requires a scientific “bridge” to the approved product (generally a bioavailability or bioequivalence study)
  - Requires patent certification/statement

What is a patent certification or statement?

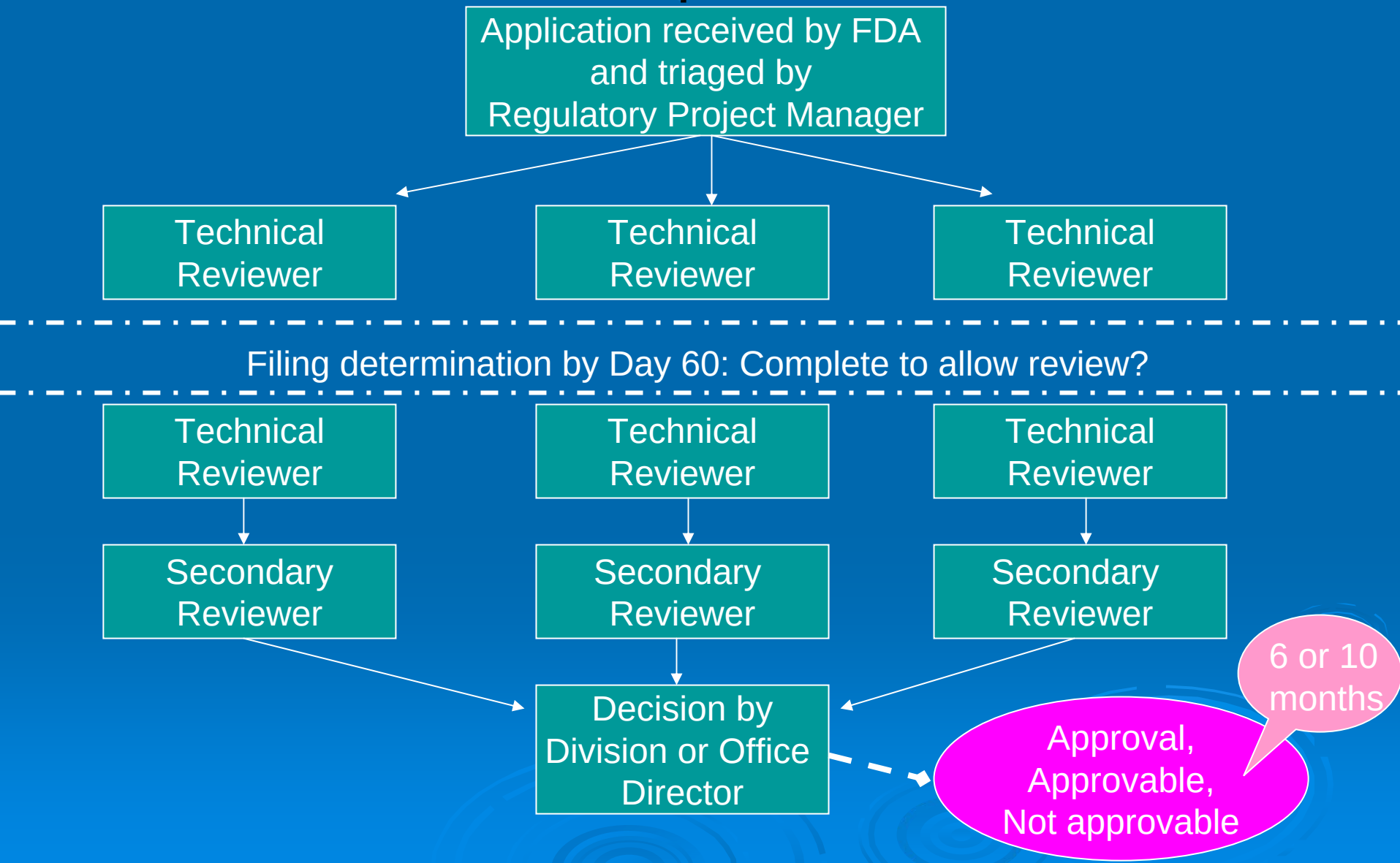
- Requires that the applicant of a 505(b)(2) application certify, to the best of their knowledge, to each patent that claims a drug relied upon to support approval of the (b)(2) product
  - Patent information submitted to FDA is found in the "Orange Book"

http://www.fda.gov/cder/ob/default.htm

  - Types of patent certifications include not submitted, expired, will expire, etc…

21 CFR 314.50(i)(1)(i)(A)

What is the review process for an NDA?



Some advice to the potential NDA applicant:

- Research available guidance documents
- Do a thorough literature search for information regarding the active ingredient in your product
- Request a meeting with the review division
  - Don't know which division?
    http://www.fda.gov/cder/cderorg/ond.htm

  Contact the Supervisory Regulatory Project Manager
  - Don't know how?
    Guidance: Formal Meetings With Sponsors and Applicants for PDUFA Products
    http://www.fda.gov/cder/guidance/2125fnl.htm

Thank you for your attention.